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Reactions of Cookson’s diketone with potassium halides in the polyphosphoric acid medium

Aim. To study the rearrangement of Cookson’s diketone by the action of potassium halides under conditions of polyphosphoric acid catalysis.

Results and discussion. Chemical behaviour of Cookson’s diketone (C_5 -trishomocubane-8,11-dione) in the reactions with potassium halides (KCl, KBr, KI) in the polyphosphoric acid (PPA) medium have been studied. When treated with the KI/PPA mixture Cookson’s diketone undergoes reduction leading to tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione. The use of KBr instead of KI leads to formal addition of HBr to the cyclobutane ring of C_5 -trishomocubane-8,11-dione and gives 3-bromotetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione. The general scheme of the cycle opening mechanism has been proposed. In the case of using the KCl/PPA mixture the reaction does not occur.

Experimental part. The structure and composition of compounds were proved by the methods of ¹H and ¹³C NMR-spectroscopy, and also X-ray diffraction analysis. Elemental analysis was performed for the compounds obtained.

Conclusions. It has been shown that hydrohalic acids generated *in situ* under the reaction conditions do not induce the rearrangement of Cookson’s diketone to the D_3 -trishomocubane system. The cyclobutane ring opening and reduction take place instead.

Key words: Cookson’s diketone; polyphosphoric acid; ring opening; C_5 -trishomocubane; reduction

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Реакції дикетону Куксона з галогенідами калію в середовищі поліфосфорної кислоти

Мета. Дослідити перегрупування дикетону Куксона під дією галогенідів калію в умовах каталізу поліфосфорною кислотою.

Результати та їх обговорення. Вивчено хімічну поведінку дикетону Куксона (C_5 -трисгомокубан-8,11-діону) в реакції з галогенідами калію (KCl, KBr, KI) в середовищі поліфосфорної кислоти (PPA). При обробці йодидом калію в середовищі поліфосфорної кислоти дикетон Куксона вступає в реакцію відновлення, яка приводить до утворення тетрацикло[6.3.0.0^{4,11}.0^{5,9}]ундекан-2,7-діону. Використання KBr замість KI приводить до формального приєднання HBr до циклобутанового кільця C_5 -трисгомокубан-8,11-діону, в результаті чого утворюється 3-бромтетрацикло[6.3.0.0^{4,11}.0^{5,9}]ундекан-2,7-діон. Запропоновано загальну схему механізму розкриття циклу. У випадку використання системи KCl/PPA реакція не відбувається.

Експериментальна частина. Структуру та склад сполук було доведено методами ¹H та ¹³C ЯМР-спектроскопії, а також рентгеноструктурним аналізом. Проведено елементний аналіз одержаних сполук.

Висновки. Показано, що галогеноводневі кислоти, що утворюються *in situ* при змішуванні галогенідів калію та поліфосфорної кислоти, замість перегрупування дикетону Куксона в похідні D_3 -трисгомокубану спричиняють відновлення каркасу з розкриттям циклобутанового фрагмента.

Ключові слова: дикетон Куксона; поліфосфорна кислота; розкриття циклу; C_5 -трисгомокубан; відновлення

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Реакции дикетона Куксона с галогенидами калия в среде полифосфорной кислоты

Цель. Исследовать перегруппировку дикетонатов Куксона под действием галогенидов калия в условиях катализа полифосфорной кислотой.

Результаты и их обсуждение. Изучено химическое поведение дикетона Куксона (C_5 -трисгомокубан-8,11-диона) в реакции с галогенидами калия (KCl, KBr, KI) в среде полифосфорной кислоты (PPA). При обработке йодидом калия в среде полифосфорной кислоты дикетон Куксона вступает в реакцию восстановления, которая приводит к образованию тетрацикло[6.3.0.0^{4,11}.0^{5,9}]ундекан-2,7-диона. Использование KBr вместо KI приводит к формальному присоединению HBr по циклобутановому кольцу C_5 -трисгомокубан-8,11-диона, в результате чего образуется 3-бромтетрацикло [6.3.0.0^{4,11}.0^{5,9}]ундекан-2,7-дион. Предложена общая схема механизма раскрытия цикла. В случае использования системы KCl/PPA реакция не происходит.

Экспериментальная часть. Структура и состав соединений были подтверждены методами ^1H и ^{13}C ЯМР-спектроскопии, а также рентгеноструктурным анализом. Проведен элементный анализ полученных соединений.

Выводы. Показано, что галогеноводородные кислоты, образующиеся *in situ* при смешивании галогенидов калия и полифосфорной кислоты, вместо перегруппировки дикетона Куксона в производные D_3 -трисгомокубана приводят к восстановлению каркаса с раскрытием циклобутанового фрагмента.

Ключевые слова: дикетон Куксона; полифосфорная кислота; раскрытие цикла; C_5 -трисгомокубан; восстановление

The rearrangement of C_5 -trishomocubane (pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane) derivatives (**1**, Fig. 1) under acidic conditions is the most general approach for the synthesis of D_3 -trishomocubanes (**2**, Fig. 1). However, the majority of the methods reported in the literature involve the rearrangement of the substituted 8-hydroxy- or 8,11-dihydroxy- C_5 -trishomocubanes (**3**, **4**, Fig. 1) [1]. The rearrangement of the corresponding ketones is still insufficiently studied [1] although both cage ketones and products of their rearrangements are potentially useful for medicinal chemistry. So far, the only satisfactory reagent for the rearrangement of ketones is chlorosulfonic acid [2–4], which has rather low tolerance of functional groups and is not too easy to handle. Moreover, in case of substituted Cookson's diketones such rearrangement often proceeds non-selectively and affords hardly separable mixtures of polysubstituted D_3 -trishomocubanes [5].

It is believed that the rearrangement of Cookson's diketone (**5**, Fig. 1) with chlorosulfonic acid involves a formal addition of HCl to the carbonyl group, further protonation and subsequent elimination of water. The cation thus formed is attacked by a nucleophile to give the D_3 -trishomocubane system [2]. This means that any other strong Brønsted acid may induce the rearrangement. Aiming to find a convenient reagent for the rearrangement we tested the reactions of C_5 -trishomocubane-8,11-dione (Cookson's diketone **5**) [6] with a series of acidic reagents.

C_5 -Trishomocubane-8,11-dione **5** was synthesized starting from commercially available quinone **6** and cyclopentadiene in two simple steps (Diels–Alder reaction and [2+2]-photocyclization) in the overall yield of 78% [6] (Scheme 1).

First, we tried to perform the rearrangement of **5** using the procedures, which previously were successfully employed for the rearrangement of diol **4** [7, 8]. Thus, diketone **5** was stirred for 16 h in hydro-

halic acids (HCl, HBr, HI) at elevated temperatures ($\approx 100^\circ\text{C}$). However, in all cases the reaction did not occur, and the started material was recovered.

At the same time, it is known that the KI/PPA system, where hydrogen iodide was generated *in situ*, was also used for the rearrangement of C_5 -trishomocubane-8,11-diol **4**. It was found that applying this literature procedure (6 h, 100–110°C) [8] to diketone **5** gave a single product isolated with the yield of 60%. Its physicochemical constants were in agreement with the literature data for tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione **8** [9]. Obviously, in this case reduction took place instead of the expected rearrangement to the D_3 -trishomocubane system (Scheme 2). However, we were pleased to find that Cookson's diketone was reactive towards KX/PPA mixtures (Scheme 2).

Considering that HI was much more active reducing agent than HBr we assumed that the use of KBr instead of KI would allow us to avoid reduction. However, tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione **8** was formed in this case too, albeit in smaller amount (30% in the crude mixture as judged by GC/MS). The main product (70% in the crude mixture) was 3-bromo-tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione **9**. Since tetracyclic bromodiketone **9** had quite similar NMR-spectra compared to the possible product with the D_3 -trishomocubane skeleton and the same molar mass, its structure was confirmed by the X-Ray single crystal structure analysis (Fig. 2). It should be noted that bromodiketone **9** was previously prepared from **5** in 3-step synthesis in the overall yield of 22% [10]. In unclear reasons, diketone **5** did not interact with KCl in the polyphosphoric acid medium even after continuous reflux (Scheme 3).

Considering the above facts and the suggested mechanisms previously reported for similar reactions [11–13] we proposed the scheme for the mechanism of the ring opening reaction. Initially, protonation of the carbonyl group takes place. The intermediate **A**

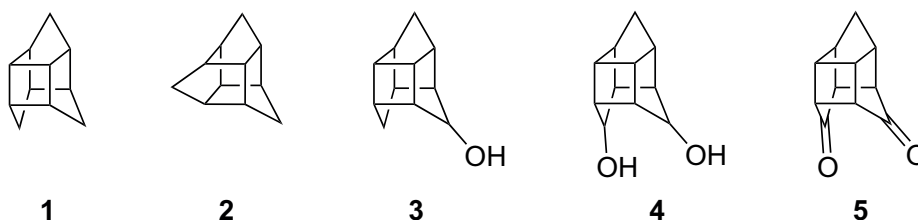
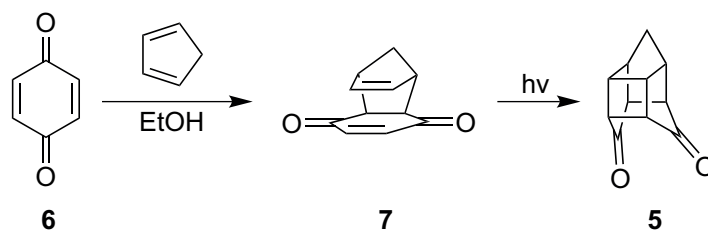


Fig. 1. C_5 -trishomocubane **1**, D_3 -trishomocubane **2**, 8-hydroxy- **3** and 8,11-dihydroxy- C_5 -trishomocubanes **4**, Cookson's diketone **5**

Scheme 1. The synthesis of C_5 -trishomocubane-8,11-dione **5**

obtained undergoes keto-enol tautomerism to form cation **B**. Under KBr/PPA conditions the cation can be either attacked by a bromide ion to form bromide **9**, or undergo reduction with HBr, while under KI/PPA conditions only reduction with HI occurs. Such mechanism would explain emergence of all the products which previously seemed to be atypical (Scheme 4).

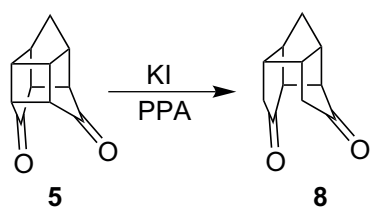
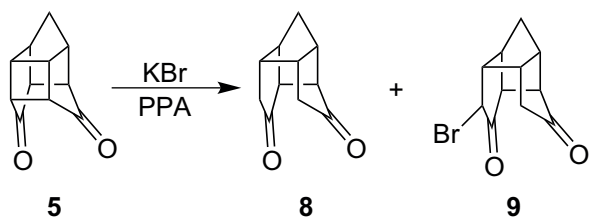
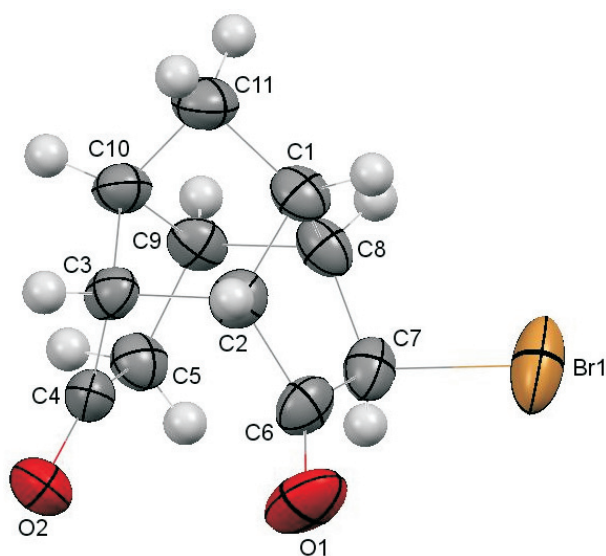
Experimental part

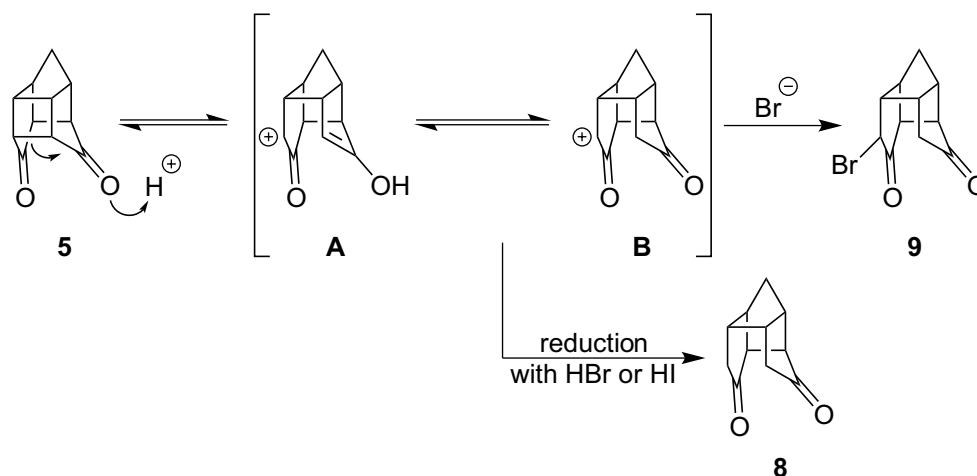
^1H and ^{13}C NMR-spectra were recorded using Bruker Avance NMR spectrometers operating at 400 and 500 MHz (101 and 126 MHz for ^{13}C experiments). Chemical shifts were reported relative to the internal standard TMS (^1H). Melting points were uncorrected. Solvents were dried before use according to standard methods. Elemental analysis was performed in the analytical laboratory of the Institute of Organic Chemistry at the NAS of Ukraine.

The reaction of C_5 -trishomocubane-8,11-dione with KI/PPA. We applied the procedure reported previously [8]. To 85% H_3PO_4 (7.80 g) in a round-bottom flask (100 mL) add P_2O_5 (5.90 g, 20.8 mmol). After the initial exothermic reaction had subsided add KI (11.2 g, 67.5 mmol) and C_5 -trishomocubane-8,11-dione **5** (2.00 g, 11.5 mmol). Fit the flask with a reflux condenser and a drying tube and stir for 6 h at

105–110°C. Transfer the cooled dark viscous mass to a separate funnel using dichloromethane and water. After extracting with dichloromethane wash the organic phase with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2×10 mL) and water (2×10 mL), dry over Na_2SO_4 , pass through a pad of Al_2O_3 , and evaporate under reduced pressure to obtain 1.23 g (7.00 mmol, 61%) of compound **8**. Physicochemical constants of compound **8** were in agreement with the literature data; M. p. = 253–256°C (lit. 255–257°C [9]).

The reaction of C_5 -trishomocubane-8,11-dione with KBr/PPA. To 85% H_3PO_4 (7.80 g) in a round-bottom flask (100 mL) add P_2O_5 (5.90 g, 20.8 mmol). After the initial exothermic reaction had subsided, add KBr (8.03 g, 67.5 mmol) and C_5 -trishomocubane-8,11-dione **5** (2.00 g, 11.5 mmol). Fit the flask with a reflux condenser and a drying tube and stir for 6 h at 105–110°C. Transfer the cooled, dark, viscous mass to a separatory funnel using dichloromethane and water. After extracting with dichloromethane, wash the organic phase with 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (2×10 mL) and water (2×10 mL), dry over Na_2SO_4 , and evaporate under reduced pressure. Subject the residue to silica gel column chromatography (hexane/ethyl acetate 5:1) to give 0.536 g (3.04 mmol, 26%) of compound **8** and 1.85 g (7.25 mmol, 63%) of compound **9**.

Scheme 2. The reaction of C_5 -trishomocubane-8,11-dione **5** with KI in polyphosphoric acidScheme 3. The reaction of C_5 -trishomocubane-8,11-dione **5** with KBr in polyphosphoric acidFig. 2. The structure of 3-bromotetracyclo[6.3.0.0.4.11.0.5.9]undecane-2,7-dione **9** according to X-ray diffraction data. Thermal ellipsoids are shown at 50% probability level



Scheme 4. The scheme of the mechanism proposed for the reaction of Cookson's diketone **5** with potassium halides in the polyphosphoric acid medium

Physicochemical constants of compound **9** were in agreement with the literature data; M. p. = 120–121°C (lit. 122–123°C) [14].

The X-ray crystal structure experimental details.

The colorless crystals of **9** (C₁₁H₁₁O₂Br) are monoclinic. At 293 K $a = 11.4462(6)$, $b = 7.5417(4)$, $c = 11.7850(5)$ Å, $\beta = 104.62(5)^\circ$, $V = 984.40(8)$ Å³, $M_r = 255.11$, $Z = 4$, space group $P2_1/n$, $d_{calc} = 1.721$ g/cm³, $\mu(\text{MoK}\alpha) = 4.144$ mm⁻¹, $F(000) = 512$. Intensities of 9086 reflections (2867 independent, $R_{int} = 0.030$) were measured on a "Xcalibur-3" diffractometer (graphite monochromated MoK α radiation, CCD detector, ω -scanning, $2\theta_{max} = 60^\circ$). The structure was solved by the direct method using a SHELXTL package [15]. The absorption correction was done using the multi-scan method ($T_{min} = 0.575$, $T_{max} = 0.682$). Positions of hydrogen atoms were located in electron density difference maps and refined using isotropic approximation. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 2835 reflections was converged to $wR_2 = 0.146$ ($R_1 = 0.053$ for 2047 reflections with $F > 4\sigma(F)$, $S = 1.086$). The final atomic coordinates and crystallographic data for molecule **9** were deposited to with the Cambridge Crys-

tallographic Data Centre, 12 Union Road, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk) and were available on request quoting the deposition numbers CCDC 1819442).

Conclusions

The reactions of Cookson's diketone with potassium halides in the polyphosphoric acid medium have been studied. It has been found that hydrohalic acids generated *in situ* under the reaction conditions do not induce the rearrangement of Cookson's diketone to the D_3 -trishomocubane system. Therefore, the use of the KI/PPA mixture for the reaction leads to reduction of the starting diketone giving tetracyclo[6.3.0.0.^{4,11}.0^{5,9}]-undecane-2,7-dione. The use of the KBr/PPA mixture leads to formal addition of HBr to the cyclobutane ring and gives 3-bromotetracyclo[6.3.0.0.^{4,11}.0^{5,9}]-undecane-2,7-dione. Though the target process is accompanied with the partial reduction and the admixture, tetracyclo[6.3.0.0.^{4,11}.0^{5,9}]-undecane-2,7-dione is also formed. Hydrogen chloride generated from KCl and PPA does not react with Cookson's diketone.

Conflict of interests: authors have no conflict of interests to declare.

References

- Levandovsky, I. A.; Sharapa, D. I.; Cherenkova, O. A.; Gaidai, A. V.; Shubina, T. E. The chemistry of D_3 -trishomocubane. *Russ. Chem. Rev.* **2010**, *79* (11), 1005-1026. <http://doi.org/10.1070/RC2010v079n11ABEH004119>.
- Sharapa, D. I.; Gayday, A. V.; Mitlenko, A. G.; Levandovskiy, I. A.; Shubina, T. E. A Convenient Road to 1-Chloropentacycloundecanes – A Joint Experimental and Computational Investigation. *Eur. J. Org. Chem.* **2011**, *2011* (13), 2554-2561. <https://doi.org/10.1002/ejoc.201001731>.
- Mishura, A.; Sklyarova, A.; Sharapa, D.; Levandovsky, I.; Serafin, M.; Fokin, A.; Rodionov, V. Stereoselective preparation of mono- and bis-derivatives of pentacyclo[6.3.0.0.2.6.0.3.10.0.5.9] undecane (D_3 -trishomocubane). *Open Chemistry* **2013**, *11* (12), 2144-2150. <https://doi.org/10.2478/s11532-013-0339-8>.
- Tolstikov, G. A.; Lerman, B. M.; Galin, F. Z.; Struchkov, Y. T.; Andrianov, V. G. Synthesis of trishomocubane and dihomobasketane derivatives via the skeletal. Rearrangement under the action of chlorosulphonic acid. *Tetrahedron Lett.* **1978**, *19* (43), 4145-4148. [https://doi.org/10.1016/S0040-4039\(01\)95166-4](https://doi.org/10.1016/S0040-4039(01)95166-4).
- Zhyhadlo, Y. Y.; Gaidai, A. V.; Sharapa, D. I.; Mitlenko, A. G.; Shishkin, O. V.; Shishkina, S. V.; Levandovskiy, I. A.; Fokin, A. A. Functionalised Cookson's Diketones in Chlorosulfonic Acid: Towards Polysubstituted D_3 -Trishomocubanes. *Journal of Chemical Research* **2017**, *41* (12), 718-721. <https://doi.org/10.3184/174751917X15125690124264>.

6. Cookson, R. C.; Crundwell, E.; Hill, R. R.; Hudec, J. 586. Photochemical cyclisation of Diels–Alder adducts. *Journal of the Chemical Society (Re-sumed)* **1964**, (0), 3062-3075. <https://doi.org/10.1039/JR9640003062>.
7. Kent, G. J.; Godleski, S. A.; Osawa, E.; Schleyer, P. v. R. Syntheses and relative stability of (D_3)-trishomocubane (pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane), the pentacycloundecane stabilomer. *J. Org. Chem.* **1977**, *42* (24), 3852-3859. <https://doi.org/10.1021/jo00444a012>.
8. Smith, E. C.; Barborak, J. C. Syntheses of the pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecyl (trishomocubyl) and tetracyclo[6.3.0.0^{4,11}.0^{5,9}]undeca-2,6-dienyl (homohypostrophenyl) systems. *J. Org. Chem.* **1976**, *41* (8), 1433-1437. <https://doi.org/10.1021/jo00870a032>.
9. Butler, D. N.; Munshaw, T. J. The synthesis of 2,3,5,6-endo,endo,endo,endo-tetrakis-substituted bicyclo[2.2.1]heptanes. *Can. J. Chem.* **1981**, *59* (24), 3365-3371. <https://doi.org/10.1139/v81-500>.
10. Kotha, S.; Manivannan, E.; Sreenivasachary, N. Allylation of caged diketones via fragmentation methodology. *J. Chem. Soc., Perkin Trans. 1* **1999**, (19), 2845-2848. <https://doi.org/10.1039/A902629K>.
11. Dobmeier, M.; Herrmann, J. M.; Lenoir, D.; König, B. Reduction of benzylic alcohols and α -hydroxycarbonyl compounds by hydriodic acid in a biphasic reaction medium. *Beilstein Journal of Organic Chemistry* **2012**, *8*, 330-336. <https://doi.org/10.3762/bjoc.8.36>.
12. Gordon, P.; Fry, A.; Hicks, L. Further studies on the reduction of benzylic alcohols by hypophosphorous acid/iodine. *ARKIVOC* **2005**, *2005*, 393-400.
13. Deno, N. C.; Friedman, N.; Hodge, J. D.; MacKay, F. P.; Saines, G. The Hydride Transfer Nature of the Reduction of Carbonium Ions by HBr, HI and a Pt and an Ir Hydride. *J. Am. Chem. Soc.* **1962**, *84* (24), 4713-4715. <https://doi.org/10.1021/ja00883a019>.
14. Pekhk, T. I.; Petrenko, A. E.; Aleksandrov, A. M.; Sorochinskii, A. E.; Golovaty, V. G.; Kukhar, V. P. ChemInform Abstract: Bromo and Hydroxy Derivatives of Tetracyclo(6.3.0.0^{4,11}.0^{5,9})undecane- 2,7-dione. *ChemInform* **1992**, *23* (36), 2560. <https://doi.org/10.1002/chin.199236121>.
15. Sheldrick, G. A short history of SHELX. *Acta Crystallographica Section A* **2008**, *64* (1), 112-122. <https://doi.org/10.1107/S0108767307043930>.

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